5, lines 4-10) and a low viscosity gel has a polymer concentration of less than 4%. (page 4, line 23, of the application).

The Examiner has rejected claims 1-22 under 35 U.S.C. § 112 first paragraph asserting that the claimed misoprostol metabolites are not enabled other than for misoprostol acid . Applicant traverses this rejection on the basis that 35 U.S.C. §112 requires that the written description of the specification be sufficient to enable any person skilled in the art to which it pertains to make and use the invention. Applicants assert that one of ordinary skill in the art would be familiar with the misoprostol metabolites. Moreover, applicants have shown throughout the specification that misoprostol acid which, is a metabolite is effective at treating sexual dysfunction in women (see for example page 3, line 17). Nonetheless to facilitate early allowance of the claims, applicant has amended the claims to specify misoprostol and misoprostol acid which, the Examiner agrees are enabled by the description of the claimed invention. Nonetheless, applicant reserves the right to prosecute claims directed to misoprostol metabolites in general in a subsequent application.

Rejection under 35 U.S.C.§102

In order for a reference to be a valid anticipation of a claimed invention, at least two requirements must be met. These are first that the reference must teach every element of the claim, and second that the reference must enable the claimed invention. (MPEP 2131 and 2131.01) The Examiner has rejected the pharmaceutical composition claims (now claims 43-47) as anticipated by the Cytotec monograph. However, the Cytotec monograph cited by the Examiner teaches a pharmaceutical composition containing misoprostol and hydroxypropyl cellulose for use in a formulation suitable for oral delivery and at an effective dose for treating gastric ulcers when taken 4 times each day with food. The Cytotec reference fails to describe a pharmaceutical composition containing an effective dose of misoprostol or misoprostolic acid in a topical formulation for application to the clitoris or vagina required in claim 43-47. The formulation of a tablet is distinct from that of a topical formulation. Moreover, an effective dose of misoprostol for systemic treatment of stomach ulcers is expected to differ from an effective dose of topical misoprostol suitable for local activity on the vagina or clitoris.

For the above reasons, the Cytotec reference does not anticipate claims 43-47 and the Examiner is respectfully requested to reverse the rejection.

Rejection under 35 USC § 103

The Examiner has rejected method claims 1-22 as being unpatentable over Nahoum, et al., and Buyuktimkin, et al. in view of El Rashidy, Lowrey and Reilly. The Examiner's remarks have been addressed with respect to new method claims 27-47 which are directed to a method for treating sexual dysfunction in a female subject in which an effective dose of misoprostol or misoprostol acid is administered in a formulation that is suitable for topical application to the clitoris or vagina in women.

Using the factual inquiries laid out by Grahame v. John Deere Co. 383 U.S.1,48 USPQ 459 (1966) which sets the standard for obviousness-(a) determining the scope and content of the prior art, (b) ascertaining the differences between the prior art and the claims in issue, (c) resolving the level of ordinary skill in the pertinent art; and (d) evaluating evidence of secondary considerations, applicants assert the present claimed methods are not obvious over the cited references whether considered singly or in combination. The references and the present independent claim 27 are summarized in the Table below.

Claimed method	Buyuktimkin	Nahoum	El-Rashidy	Reilly	Lowrey
formulation for application to clitoris or vagina	transdermal uptake	intraurtheral or parenteral	penis surface		oral administratio n
misoprostol or misoprostol acid as primary agent	PGE_1 as primary agent	H3 agonists as primary agent	isoquinoline ethers	gelatin	phentolamine
secondary agent	use of enhancers to enhance skin penetration	secondary therapeutically active compound and enhancer	use of enhancer, cites cyclodextrin as enhancer		rapidly dissolving form
sexual dysfunction	peripheral vascular disease	erectile dysfunction	male impotence	coating for pills and capsules and as an emulsifying agent	male and female sexual response

(a) The scope and contents of the prior art do not suggest the present claimed methods.

Of the cited references, only Nahoum, et al. mentions the prostaglandin, misoprostol (column 10, line 1) but does not differentiate between misoprostol and a second prostaglandin, alpostradil even though alpostradil does not have the important advantages of misoprostol (Fotinos declaration paragraph 3; and the application, page 2).

In addition, although Nahoum, et al. suggests that H3 agonists and a second vasoactive agent may be used to treat men and women (column 9, line 46), the reference fails to provide an enabling disclosure as to how to treat women for sexual dysfunction. The generic description of topical formulations in column 10, line 65; column11, line 47 and enhancers (column 14, line 9; column 15, line 60) does not provide specific guidance to one of ordinary skill in the art as to how these reagents should be used and to what effect. For example, the use of ethanol is described in column 11, line 38 and 51, yet ethanol in inappropriate amounts could be extremely painful when applied to clitoris or vagina. Dimethyl sulfoxide (DMSO) is recommended as an enhancer (column 14, line 42) yet DMSO is also problematic[1].

Applicant asserts that because an enormously broad range of formulations and active ingredients are proposed in the reference, one of ordinary skill in the art might

[1] "..this carrier [DMSO] has not been approved for use by the U.S. Food and Drug Administration. Moreover, DMSO also has the undesirable effect of enhancing the systematic absorption of the vasodilator" (El-Rashidy: col 2, line 51-58)

preferentially look to the 13 examples for guidance. Indeed none of the 13 examples suggest the use of prostaglandins and provide no motivation for using prostaglandins for treating sexual dysfunction.

Although the reference discusses topical administration in general terms, this refers to intraurethral administration in men (Examples 2-13), a route of administration that is anatomically unfeasible for women. The examples also describe intravenous (Example 1 and column 24, lines 19-67) which is outside the scope of the present claims.

In summary, the Nahoum reference does not provide any suggestion as to how prostaglandins in particular misoprostol might be administered to women topically on the clitoris or vagina or indeed anywhere for treating sexual dysfunction.

Buyumtkin, et al. describes various techniques for increasing transdermal uptake of prostaglandin E1 (PGE_1) to treat peripheral vascular disease in general (column 1, line 28) although sexual dysfunction in particular is not described. The reference in column 2, line 56, refers to the Merck Index for a description of uses. The Merck Index (12^{th} Edition) describes use of prostaglandin E_1 for neonatal cardiac problems, and in non-atherosclerotic vasculopathy. There is no specific suggestion that prostaglandins be applied topically to the vagina or clitoris in women for treating sexual dysfunction. (Exhibit D)

Moreover, the reference suggests that in November 1997, there were no effective topical compositions containing prostaglandin E1:

> While the potential benefits from transdermal delivery of prostaglandin E1 have long been recognized, prior efforts at developing a topical composition for prostaglandin delivery have not been fully successful. (column 1, lines 29-33)

It is important to realize that this reference does not seek to demonstrate that an effective amount of a prostaglandin can be administered topically to a human subject. The reference is directed specifically and only to increasing the amount of the compound that can cross the skin. To analyze penetration of PGE_1, the reference utilizes an *in vitro* snake skin model. No data is provided to demonstrate efficacy for any treatment let alone sexual dysfunction in women. There is no recognition by the reference that instead of studying uses of enhancers to increase penetration of PGE1, significantly better results might be obtained with misoprostol. It is apparent from Buyuktimkin, et al. that the

reference was not aware of the superior absorptive properties of misoprostol over PGE_1 and there was no suggestion in the reference that misoprostol should be used for any purpose let alone sexual dysfunction.

El- Rashidy describes the use of topical compositions of isoquinoline ethers for treatment of male impotence. "The peripheral vasodilators preferred for the present purpose are isoquinolines" (column 4, lines 6-8)

The reference does not suggest or teach the use of misoprostol for treating sexual dysfunction in women. Whereas the reference does teach topical compositions for treating males, these topical compositions do not include misoprostol or even prostaglandins. The reference describes the use of isoquinoline ethers together with a pharmacologically acceptible enhancer cyclodextrin formulated in a gel for topical delivery. It appears that the Examiner has selected this reference solely because the use of cyclodextrin as an enhancer, most preferably hydroxypropyl-β cyclodextrin (HPBCD) enhances uptake of the preferred isoquinoline ethers vasoactive agents. However, the present claimed method utilizes α-cyclodextrin to reduce side effects and permit high doses of misoprostol to be administered to the clitoris or vagina (Application page 6, line 20 and dependent claim 15). There is no basis to conclude from the reference describing cyclodextrin enhancing uptake of isoquinoline ethers that cyclodextrin may also reduce potential side effects of misoprostol. Even with impermissible hindsight, the use of cyclodextrin to reduce side effects of misoprostol could not have been determined from the El Rashidy reference.

Lowrey teaches the oral administration of phentolamine, which is an adrenoreceptor blocker used by Nahoum, et al. with an H3 agonist to treat sexual dysfunction. The Examiner has identified a section of the Lowrey reference that gives a medical text book description of the normal pre-orgasmic sexual response in females. (column 4, lines 53-54). This passage suggests nothing about how a therapeutic agent for treating sexual dysfunction might be administered to a female patient who suffers from sexual dysfunction.

The Examiner's has asserted that

> it is known in the art that female sexual response is associated with vasodilation and engorgement of the genitalia with arterial blood. Therefore applying a composition containing known vasodilating agents, including the instant

compounds directly onto any area of the genital would have reasonably expected to be effective in treating female sexual dysfunction. (Office action Paper 6, Page 6)

Contrary to the above assertion, although the male pre-orgasmic response has been determined to be similar to that of females, this has not resulted in topical application of compounds other than via the urethra. Unfortunately, the urethra is not a convenient route of administration for women despite the commonality of the female and male sexual response. Moreover, even for men, the urethra is less then perfect solution involving devices for inserting medication. The alternative to urethral administration presented by Nahoum, et al. is self-injection into erectile tissue to achieve an adequate response (also see background to the El-Rashidy reference).

Reilly describes the use of gelatin to coat pills and form capsules and as a vehicle of suppositories. It is recommended as an emulsifying agent and has been used as an adjuvent protein food in malnutrition. This however has no relevance to the present claimed invention other than the fact the gelatin is included in the formulation. A reference that describes gelatin as a food product does not suggest the claimed invention.

(b) The recited references do not enable one of ordinary skill in the art to combine the references so as to suggest the claimed methods and secondary considerations relating to clinical trials are provided

The Examiner has determined that one of ordinary skill in the art would have been motivated to combine the five recited references to describe the present invention. However, applicant asserts that there is no such motivation and that even if all five references were combined, this would not lead one of ordinary skill in the art to enable the present claimed invention without the guiding hand of hindsight. The above Table highlights the different focus of each of the cited references so that even if they were combined, they would not teach the required elements of the claimed method and composition.

The Examiner states on page 6 of the action

It would have been obvious for one of ordinary skill in the art at the time the invention was made to apply a topical female sexual dysfunction treating composition of misoprostol with or without another vasodilator onto the vagina or clitoris.

The applicants believe that the Examiner has disregarded the problems in the field of sexual dysfunction in women for which the claimed novel method provides a new source of hope for sufferers.

The applicants have appreciated that women have a problem with sexual dysfunction and that the female anatomy precludes the use of intraurethral applications of vasodilatory agents. The applicants appreciated the importance of topical delivery of active agents for treatment of erectile dysfunction.

It is widely stated in the prior art that one important problem of topical administration of vasoactive compounds is to getting reasonable penetration of the skin or mucosa by the agent. (El-Rashidy, col 2, line 59[2]) There is a particular problem of skin or mucosal penetration with certain vasoactive compounds such as the conventionally used prostaglandins.

> While the potential benefits from transdermal delivery of prostaglandin E1 have long been recognized, prior efforts at developing a topical composition for prostaglandin delivery have not been fully successful. (Buyuktimkin, column 1, lines 29-33)

For this reason, efforts have gone into finding suitable enhancing agents that may be approved for use and which do not cause too much systemic uptake of the vasoactive agents (El-Rashidy, column 2, line 57[3]). Systemic uptake such as occurs during oral administration is not desirable both because in general an effect is desirable over a short period of time and secondly because vasoactive agents can have undesirable side effects where the subject has a cardiovascular problem.

None of the references either alone or combination have identified the particular properties of misoprostol or misoprostol acid which make it a particular useful agent for treating sexual dysfunction. These properties include the ability to induce a strong local vasodilation and ease of penetration of the skin and mucosa without requiring additional permeation enhancers. This is described in the application on page 2, line 20 and page 3 lines 10-26.

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[2] The problem with topically administered drugs is their limited penetration of the drug through skin (col 2, line 59)

"...we have a big penetration of misoprostol..." (page 2, line 22)

"Misoprostol-compared to other vasodilatory drugs (eg nitroglycerin, prostaglandin E_1 etc.) cause a strong local vasodilation " (page 3, lines 10-12)

"Misoprostol can be dissolved in water and its compatibility with excipients provides the opportunity of production of a variety of simple pharmacotechnical forms for external use which are at the same time very well tolerated by the skin and the mucosa. (page 3, lines 23-26).

The only one of the cited references that mentions misoprostol is Nahoum, et al. However, as discussed above, Nahoum, et al. does not suggest that misoprostol might have properties that would make it a much better active agent than alpostradil nor would Nahoum receive any inspiration in this regard from the Cytotec reference which describes an oral formulation of misoprostol for treating ulcers.

Given the preferred use of PGE_1 or alpostradil in the prior art even with the acknowledged problems of permeability (Buyuktimkin, column 1, lines 29-33, Nahoum, et al. column 19, lines 6-23) one of ordinary skill in the art would not have been motivated to use misoprostol instead of PGE_1.

The significance of selecting misoprostol over alpostradil is highlighted in the accompanying declaration (Exhibit B) which provides clinical data in men that demonstrates the dramatically increased beneficial effects of a formulation containing misoprostol compared with a formulation containing PGE_1. Exhibit C provides additional secondary material in the form of a press release reporting the disappointing effects of a product, Topiglan, being commercialized for men which relies on topical application of alpostradil.

In summary, there was no teaching in the prior that provided motivation for one of ordinary skill in the art to select misoprostol or misoprostolic acid as a primary compound for the topical treatment of erectile dysfunction in women.

Applicant submits herewith an additional reference in a supplemental information disclosure statement. This reference US 6,046,240 describes methods for treating female sexual dysfunction using PGE1. There is no suggestion in this reference that misoprostol be utilized. Instead, the reference relies on prostaglandins with much poorer skin

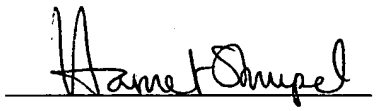
[3] Moreover, DMSO also has the undesirable effect of enhancing the systematic absorption of the vasodilator (col 2, line 57)

penetration and solubility properties. The present claimed invention is thus a significant patentable improvement over this reference.

Conclusion

For the above reasons, all claims presently in the application are believed to be allowable over the art of record and early notice to that effect is respectfully requested. Applicants request the courtesy of a phone call from the Examiner to resolve any further outstanding issues if they arise so as to expedite the above case to allowance. Applicants petition for an extension of two months according to 37C.F.R.1.17. Please charge any additional fee required for the timely consideration of this application to Deposit Account No. 19-4972.

Respectfully submitted,



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